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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,254	09/26/2005	Manuela Villa	17719 (PC27263A)	1404
23389	7590	12/07/2006		
SCULLY SCOTT MURPHY & PRESSER, PC 400 GARDEN CITY PLAZA SUITE 300 GARDEN CITY, NY 11530			EXAMINER RAHMANI, NILOOFAR	
			ART UNIT	PAPER NUMBER
			1625	

DATE MAILED: 12/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/522,254	Applicant(s) VILLA ET AL.	
	Examiner Niloofer Rahmani	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 September 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-30 are pending in the instant application.

Priority

2. This application is filed on 09/26/2005, which is a 371 of PCT/EP03/07000, filed on 07/01/2001, which claims benefit of 60/398,122, filed on 07/25/2002.

3. ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 30 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. V. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). These claims are withdrawn from consideration.

4. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 provides for the use of compounds as claimed in any of the claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

5. Claims 19-20, and 24 are rejected because the terms "diazotation, subsequent appropriate quenching, suitable solid support" are confusing. What do diazotation, subsequent appropriate quenching, suitable solid support mean? Correction is required.

6. Claim 25 is rejected because the terms "a library of two or more compounds of formula (I)" is confusing. What does a library of two or more compounds of formula (I) mean? Does it mean pharmaceutical composition? Correction is required.

7. Claim 28 is rejected because the terms "a product" is confusing. What does a product mean? Does it mean a pharmaceutical composition or a compound? Correction is required.

8. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject

matter that was not described in the specification in such a way to convey reasonably to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification lacks written description of the claim i.e. "diazotation and subsequent appropriate quenching". No information was found in the specification that how the formula (II) can be diazotated and subsequent appropriate quenched to obtain a compound of formula (I). Therefore, the specification lacks description of "diazotation and subsequent appropriate quenching".

9. Claims 20, and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way to convey reasonably to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification lacks written description of the claim i.e. "suitable solid support". No information was found in the specification showing how a compound of formula (I) can react with a suitable solid support to obtain a compound of formula (III). Therefore, the specification lacks description of "suitable solid support".

10. Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification lacks enablement of the terms "diazotation and subsequent appropriate quenching", which are claimed in the process claims. They do not enable how to diazotate and subsequent quench formula (II) to a compound of formula (I). Therefore, the specification lacks enablement for the terms "diazotation and subsequent appropriate quenching".

11. Claims 20 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification lacks enablement of the term "a suitable solid support", which are claimed in the process claims. They do not enable what kind of a suitable solid support can be used to react with a compound of formula (I) to obtain a compound of formula (III). Therefore, the specification lacks enablement for the term "a suitable solid support".

12. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims.
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to a method for treating diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative, disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders using a pyrazole-tetrahydro pyridine derivative represented by formula (I).

The state of the prior art: Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn

specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative, disorders,

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Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

Amount of guidance/working examples: On pages 32-41 of the specification, applicant has examples of test compounds for inhibition assay of cdk2/Cyclin A activity. However, applicant has not guidance or examples for treating diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative, disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders using a pyrazole-tetrahydro pyridine derivative represented by formula (I).

The breadth of the claims: The breadth of claims is drawn to a method for treating diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative, disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders using a pyrazole-tetrahydro pyridine derivative represented by formula (I).

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative, disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders using a pyrazole-tetrahydro pyridine derivative represented by formula (I), one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 1-12, for treating diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative, disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders using a pyrazole-tetrahydro pyridine derivative represented by formula (I), have been enabled by the instant specification.

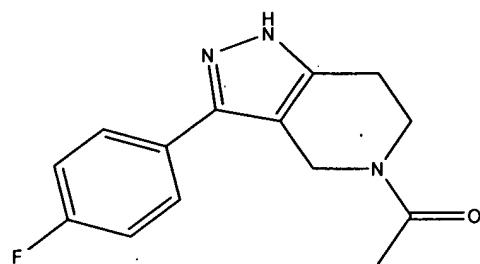
13. *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-18, 21-23, and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Winters et al. US 4,500,525. Winters et al. disclosed the instant claimed compounds and compositions on column 9, EXAMPLE 1, 5-acetyl-3-(4-fluorophenyl)-4,5,6-7-tetrahydro-1H-pyrazolo[4,3-c]pyridine



, which the compounds of the invention

posses cardiogenic, antihypertensive, CNS depressant, neuroleptic, and analgesic activity. Therefore, the instant claim is anticipated by Winters et al.

14. Double Patenting

Claim 29 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 13. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The preamble does not give patentable weight to the claim.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas Mckenzie, can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR

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only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI

12/04 /2006

NK



D. MARGARET SEAMAN

PRIMARY EXAMINER

GROUP 1625